Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
F555PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/005986	26.04.2004	28.04.2003
International Patent Classification (IPC) or national classification and IPC		
Applicant		
SEKISUI CHEMICAL CO., LTD.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1,2,4-31 as originally filed/furnished

pages* 3 received by this Authority on 28.02.2005

pages* _____ received by this Authority on _____

☒ the claims:

nos. 2-11 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1,13 received by this Authority on 28.02.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/1 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, nos. 12

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 13

because:

☒ the said international application, or the said claims Nos. 13
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 13 includes an embodiment relating to methods for treatment of the human body by therapy, and thus this International Searching Authority is not required to carry out international preliminary examination on this subject matter under the provisions of PCT Article 34(4)(a)(i) of the PCT and PCT Rule 67.1(iv).

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 13

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-11	NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: JP 61-277628 A (Asahi Chemical Industry Co., Ltd.), 8 December 1986, entire document; claims; page 2, lower left column, 2nd line from the bottom to page 3, upper left column, 2nd line from the bottom; examples (Family: none)

Document 2: JP 60-120821 A (Asahi Chemical Industry Co., Ltd.), 28 June 1985, entire document & EP 147689 A2 & JP 60-252423 A & JP 61-85317 A & JP 61-87671 A & JP 61-93121 A & JP 61-93122 A & US 4839290 A

Document 3: Wilkinson, K.A. et al., 'Enhancement of the human T cell response to culture filtrate fractions of Mycobacterium tuberculosis by microspheres', J. Immunol. Methods, (2000), Vol. 235, No. (1-2), pages 1 to 9

Document 4: JP 63-160578 A (Asahi Chemical Industry Co., Ltd.), 4 July 1988, entire document; claims; page 2, lower left column to page 4, lower left column (Family: none)

Document 5: JP 61-100522 A (Toray Industries, Inc.), 19 May, 1986, entire document; claims; page 2, lower left column to page 3, upper left

column, examples (Family: none)

Document 6: JP 63-203623 A (Toray Industries, Inc.), 23 August, 1988, entire document; claims; page 2, lower right column to page 3, lower left column; examples (Family: none)

Document 7: Kazutoshi Yamazaki et al.,' Shushu no Kobunshi Oyobi Hyomen Arasa o Yusuru Zairyo ni Okeru Zen Kecchu no Karyukyu Kyuchaku Kyodo no Kento', Polymer Preprints, Japan, (1991), Vol. 40, No. 7, pages 2230 to 2232

Document 8: Kazuo Niimura et al., 'Somen Sakusan Cellulose Beads no Shuyo Eshi Inshi Yuki Sayo', The Japanese Journal of Artificial Organs, 1993, Vol. 22, No. 5, pages 1233 to 1237, entire document, page 1234, left column, III.1., page 1235, left column, 2nd line from the bottom to page 1236, the last line

Document 9: JP 6-209992 A (Sekisui Chemical Co., Ltd.), 2 August 1994, entire document; claim 1; page 3, column 4, paragraph [0016] to page 4, column 5, paragraph [0027] (Family: none)

Document 10: Yasuhito, A. et al., 'The endogenous induction of tumor necrosis factor serum (TNS) for adjuvant postoperative immunotherapy of cancer, -changes in immunological markers of the blood- ', Japanese Journal of Surgery, 1990, Vol. 20, No. 1, pages 19 to 26

Document 11: Akira HAYASHI, 'Gan Men'eki Ryoho no Atarashii Tenkai - Shoki Men'eki to Kakutoku Men'eki no Kakehashi to shite no BCG-CWS',

Molecular Medicine, 1999, Vol. 36, Special Extra Issue, pages 220 to 229, entire document, particularly page 223, right column, line 5 to page 224, left column, line 1

Document 12: Yoshiki Ryoma, 'Hitokuiteki Koakusei Shuyozai Sonogo no Tenkai OK-432 (Picibanil) Sonogo no Tenkai', Biotherapy, 2000, Vol. 14, No. 9, pages 877 to 885

Document 13: Fujimoto, T. et al., 'Streptococcal preparation OK-432 is a potent inducer of IL-12 and a T helper cell 1 dominant state', J. Immunol., 1997, Vol. 158, No. 12, pages 5619 to 5626

Documents 1 to 6 indicate that a system is constituted by applying a substance originating from bacteria typified by microbes belonging to Mycobacterium or OK-432, together with a water-insoluble support, and by applying this system to a material such as blood, the activity of immune system cells in the material is heightened.

It would have been known to a person skilled in the art that an immuno-activating substance such as BCG or OK-432 has an effect of increasing cytokine induction such as IFN-γ and IL-12 in immune system cells, and that said capacity to increase induction of cytokine production contributes to the treatment of cancer, as described in documents 10 to 13. Therefore a person skilled in the art would be capable of predicting that the remarkable anti-cancer activation of immune system

cells offered by the supported-bonded OK-432 disclosed in document 1 would be mainly based on the remarkable increase in cytokine induction in said immune system cells.

Moreover, documents 1 to 6 do not specifically indicate that a support with porous properties is used particularly, but it would naturally be easy for a person skilled in the art to predict that if the surface area is increased in a support such as that set forth in documents 1 to 6 would result in a corresponding improvement in the effectiveness of contact with a cytokine-inducing compound and/or white blood cells in blood, thereby further increasing the cytokine inducing effect. In fact, it was a widely known technique in common practice at the time of filing of this application to increase the irregularities in the support surface, thereby improving the induced production of cytokine in blood materials and the like which said support surface is made to come into contact with, as set forth in documents 7 to 9. It would therefore be easy for a person skilled in the art to conceive of attempting to employ a known porous support as the water-insoluble support set forth in documents 1 to 6, while expecting a further activation of immune system cells or an improvement in cytokine induction.

In addition, including such an immune system cell activating substance (corresponding to cytokine-inducing agent)-porous support system in an appropriate container to constitute a device or equipment would merely be common practice to a person skilled in the art without reference to prior art documents, and this feature is not acknowledged to constitute a particular difference in

configuration.

Therefore, the inventions set forth in claims 1 to 11 do not involve an inventive step in the light of a combination of one of documents 1 to 6, one of documents 7 to 9, and one of documents 10 to 13.

The embodiments of the description of this application indicate, together with data, that a remarkable improvement in the cytokine-inducing effect is observed when a cytokine-inducing agent is used in conjunction with an insoluble support, compared to when a cytokine-inducing agent is used alone, or when an insoluble support is used alone. However, in light of the facts that

(i) The combined use of an immune system cell activating substance corresponding to a cytokine-inducing agent and an insoluble support per se, and that the combined use remarkably activates immune system cells per se, were known at the time of filing of this application, as described in documents 1 to 6, and

(ii) As described above with regard to documents 10 to 13, the remarkable activation in immune system cells in (i) and a remarkable increase in the cytokine induction capacity by said immune system cells are acknowledged to be closely related effects,

the remarkable effect relating to the aforementioned combined use asserted by the applicant is an effect which would be easily accomplished by a person skilled in the art in the light of disclosures and suggestions of prior art documents.

In addition, even with reference to the comparative testing data provided in the description, it is not

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

immediately apparent how an advantageous effect which would be unexpected by a person skilled in the art is offered by the combined use of a specific fine pore distribution as a porous support, for example.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 03/37375 A1	08.05.2003	31.10.2002	02.11.2001

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The invention according to claim 1 relates to an instrument for inducing a cytokine comprising, as the active ingredient, a compound defined by a desired property "a cytokine-inducing agent". Although claim 1 includes any compounds having this property, it appears that only a small part of the claimed compounds are supported by the description within the meaning of PCT Article 6 and disclosed therein within the meaning of PCT Article 5.

Even though the common technical knowledge at the point of the application is taken into consideration, the scope of the compounds with the property "a cytokine-inducing agent" cannot be specified. Thus, claim 1 does not comply with the requirement of clarity within the meaning of PCT Article 6.

Such being the case, the written opinion was formed based on a search which was carried out mainly on prior art concerning cytokine-inducing instruments with the use of BCG, OK-432 or other microbial cells and/or microbial cell components, which were employed in practice in the description of this application, as "a cytokine-inducing agent" together with water- insoluble supports.